1. Upon review and reconsideration, the Finality of the previous Office Action is withdrawn.

2. The Appeal Brief filed March 11, 2003 (Paper No. 23) in response to the Office Action of November 16, 2001 (Paper No. 17) is acknowledged and has been entered. Previously pending claims 25, 28, 31-36 are currently being examined.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. The following rejections are maintained.

Claim Rejections - 35 USC § 112

5. Claims 31-32 remain rejected under 35 USC 112, second paragraph for the reasons previously set forth in Paper No. 17, Section 5, page 4.

Applicant argues that in light of the teachings of the prior art and of the particular application disclosure the meaning of the term "chimeric" is broad but not indefinite. Applicant argues that Examiner pointed out that the term chimeric is art recognized to be a class of molecules. Applicant points out that as described at pages 9-10 a chimeric molecule **may** (emphasis added) include several types of molecules. Further examples of VLA-4 targeting moieties are described. The argument has been considered but has not been found persuasive because as set forth in Paper No. 10, section 10, pages 10-11, the exact meaning of the term "chimeric" is unknown, although Examiner discloses some of the possible molecules that are encompassed by the term, the term is not limited to those molecules. Further, although the specification recites that chimeric molecules may include several types of molecules, this definition is not limiting. Because the term

is not defined by the claim and the specification does not provide a standard for ascertaining the limits of the term, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The rejection may be obviated by amending claim 31, for example, to delete the phrase "wherein the fibronectin polypeptide is a component of a chimeric molecule" and substitute "wherein the fibronectin polypeptide is conjugated to a toxin and/or a peptide which increases solubility or *in vivo* life time of the fibronectin", support for which may be found on page 9.

6. Claims 25, 28 and 31-36 remain rejected under 35 USC 112, second paragraph for the reasons previously set forth in Paper No. 17, Section 6, pages 4-5.

Applicant argues that the patentee is free to be his or her own lexicographer and that it is clear from the plain language of claim 25 that the phrase "treatment of insulin dependent type I diabetes" refers to a broad range of stages of diabetes including prediabetic mammals and mammals having partial beta cell destruction and what Examiner deems to be the definition of type I diabetes is defined in the specification as the "overt diabetes" and "diabetes onset" defined in the specification.

The argument has been considered but has not been found persuasive because Applicant has clearly been his or her lexicographer. On page 1, lines 24-36, Applicant defines the stages of development of type I diabetes wherein overt diabetes, diabetes onset or clinical manifestation of disease characterized by hyperglycemia is stage 5. Further, applicant has defined "prediabetic" as an individual at risk for development of diabetes disease at any stage in the disease

process prior to overt diabetes or diabetes onset. Clearly, since prediabetic is drawn to an individual prior to diabetes onset, the claims are indefinite as currently constituted because the claims are drawn to a method of treating, type I diabetes prior to onset of disease.

Applicant further argues that it is clear from the teachings of the specification that the term "diabetes" refers to any stage of the disorder ranging from a prediabetic to an individual with "overt diabetes" manifested clinically by hyperglycemia. The argument has been considered but has not been found persuasive because the specification clearly defines prediabetic as a stage in the development of the disease prior to diabetes onset. The teachings of the specification makes it clear that diabetes development occurs over a period of time, however, the specification does not teach that the term "diabetes" refers to any stage of the development of the disorder.

Further, it is noted that the present invention in particular provides a method for the prevention of insulin dependent diabetes comprising administering to a prediabetic individual a VLA-4 blocking agent which includes fibronectin (p. 5, lines 1-20). It is very clear from the teaching of the specification that a prediabetic individual does not have insulin dependent diabetes. Although the specification recites a method of treatment of diabetes by administering into a mammal, including a human with a susceptibility to diabetes (which reads on genetic susceptibility and prediabetes) a VLA-4 blocking agent which includes fibronectin (p. 5, lines 8-20), the specification also states that genetic susceptibility is a necessary but insufficient condition for the development of the disease (p. 1, lines 26-27). Thus, it is clear that

these conflicting statements are confusing and therefore they make the claims as currently constituted, indefinite. While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term, In re Hill, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). No one skilled in the art would believe that it would be more likely than not that a disease that is not present in an individual can be treated.

The rejection may be obviated by amending claim 25, for example to delete reference to treatment of insulin dependent (type I) diabetes and substitute therefor, "a method of delaying onset of insulin dependent diabetes".

7. Claim 36 remains rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 17, Section 8, page 8 and further for the reasons set forth below.

Applicant argues that the particular sites of fibronectin involved in interaction with VLA-4 were known to be located in the alternate spliced type IIICS or V region. The argument has been considered but has not been found persuasive because the Applicant is arguing limitations not recited in the claim as currently constituted, the claim is not drawn to an alternate spliced type IIICS but rather to a non-type III CS. The argument has not been found persuasive and the rejection is maintained.

8. Claims 31-32 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper No. 17, Section 9, pages 8-9.

A review of the Appeal Brief did not appear to reveal any arguments drawn, in particular, to the rejection of claims 31-32 under 35 USC 112, first paragraph

recited above. Because Applicant did not distinctly and specifically point out the supposed errors in the rejection, the rejection is maintained.

New Grounds of Objection

9. The specification is objected to and claim 28 is objected to because they recites the sequence EILDV but do not include a sequence identifier with the sequence. Applicant is directed to 37 CFR 1.821(d) wherein it is stated that

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Appropriate correction is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

10. Claims 25, 28, 31-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for the treatment of insulin dependent diabetes comprising administering to a prediabetic mammal or a mammal having partial beta cell destruction a composition comprising a soluble fibronectin polypeptide in an amount effective to treat diabetes. This includes the treatment of diabetes in mammals, humans, that don't have diabetes and treatment of diabetes in

mammals, humans, with clinical diabetes. The specification teaches that treatment protocols after onset of disease are particularly problematic since at the time diabetes is diagnosed in humans, insulitis (which is the selective targeting and destruction of beta cells by an inflammatory cellular infiltrate of the pancreas) has typically progressed to a loss of more than 80% of the beta cells and so few beta cells may be present that even with prevention of further beta cell destruction they cannot maintain a non-diabetic state over time (p. 3). Further, diabetes onset or clinical manifestation of the disease is at Stage V of development when approximately 90% of pancreatic beta cells are destroyed (p. 1, lines 31-35). The specification teaches that there has been little success in treating human diabetes and there is a need for immunosuppressive components for use in the prediabetic stage (page 4). The specification further teaches that a key role in the development of diabetes is generally recognized for self-antigen reactive T cells and that in addition to T lymphocytes, insulitis is characterized by macrophages, dendritic cells and B cells, thus autoimmune diabetes relies upon both cellular migration and immune stimulation of newly resident cells. Cell trafficking to inflammatory sites is regulated by VLA-4 on the surface of lymphocytes and macrophages and by its counter-ligand VCAM on vascular endothelium and dendritic cells. Functional data indicates a role for VLA-4 in T cell activation and development. In additional, VLA-4 binds to fibronectin. The ability of VLA-4 to control cell migration to inflammatory sites *in vivo* has been directly demonstrated with monoclonal antibodies to VLA-4 (p. 2, lines 3-32). Current treatment protocols suggested for type I diabetes have included immunomodulatory drugs, wherein T cell activation

and development are impaired. A long prediabetic period with immunologic abnormalities and progressive beta cell destruction suggests that it may be possible to halt beta cell loss with immune intervention (p. 3, lines 13-22). Since immunosuppressive mechanisms may prevent insulitis and/or diabetes, there is a need for immunosuppressive components for use in the prediabetic stage, in particular, there is a need for compounds which inhibit entry of effector cells into the pancreas or function of those cells which have already entered the islets (p. 4, lines 20-24). It has been surprisingly discovered that administration of anti-VLA-4 antibody reduced the incidence of diabetes in the NOD mouse model of diabetes (p.4, lines 25-26).

The specification teaches that female NOD mice are diabetic at 13-20 weeks (page 16). The specification exemplifies the delayed onset of diabetes in NOD mice with an anti-VLA-4 antibody wherein the antibody is administered at four weeks (see Example 4, page 23) as well as an adoptive transfer experiments wherein spleen cells from diabetic NOD mice were pretreated with VLA-4 antibody or VCAM-Ig fusion protein prior to administration to 8 week prediabetic NOD mice (p. 23), wherein the antibody or VCAM construct were injected every 2-3 days for 12/17 days after original injection for maximal coating of VLA-4 positive cells *in vivo* (p. 10, lines 26-28). Figure 1, drawn to adoptive transfer experiments for anti-VLA-4 antibody reveals onset of diabetes at day 12 after transfer in 40% of the NOD mice whose donor cells had been not been pretreated with any antibody and that by day 21, 60% of these mice had developed diabetes. In those mice whose donor cells had been pretreated with a non-specific isotype matched antibody, 20%

of the mice developed diabetes at day 12 after transfer, at 15 days that number remained the same and 55% had developed diabetes by day 25. In contrast, only 10% of the mice whose donor cells had been treated with the anti-VLA-4 antibody developed diabetes at days 27-30. At 35 days after cells had been injected into other animals, that is at 13 weeks, control animals, injected with PBS had not developed diabetes (it is noted that the specification teaches that NOD mice develop diabetes at 13-20 weeks). In comparison, Figure 7 drawn to the VCAM-Ig fusion protein experiments revealed that 20% of the mice whose donor cells had been pretreated with irrelevant construct developed diabetes at day 12 after transfer and that 60% of the mice whose donor cells had been pretreated with irrelevant construct developed diabetes by day 15 after transfer. Of the mice whose donor cells had been pretreated with the VCAM Ig construct, 20% developed diabetes by day 24 and 60% had developed diabetes by day 30. As seen with the antibody experiments, at 35 days after cells had been injected into other animals, that is at 13 weeks, control animals, injected with PBS alone had not developed diabetes. The specification states that treatment with VCAM 2-D IgG fusion protein significantly inhibits the onset of diabetes in recipients of donor cells with 60% incidence by day 30 post transfer compared to recipients of untreated donor cells (wherein 60% of those animals developed diabetes at 21 post transfer) as compared to recipients of donor cells treated with irrelevant construct which had already achieved 60% incidence by day 15 post transfer (p. 29, lines 19-25).

One cannot extrapolate the teaching of the specification to the enablement of the claims, for treating insulin dependent diabetes in either a prediabetic mammal or

a mammal with partial beta cell destruction because the specification does not teach how to treat insulin dependent diabetes. The *in vivo* data presented is not drawn to treating mammals with diabetes since the examples are drawn to methods of delaying onset of diabetes. Wherein Example 4 is drawn to a method of delaying onset in a spontaneous diabetes model with an anti-VLA4 antibody and exemplifies the successful delay of onset with anti-VLA4 antibodies, this example is not commensurate in scope with the claimed invention since the claimed invention is not drawn to treatment with an antibody but rather is drawn to treatment with a fibronectin polypeptide. The specification clearly teaches that it has been surprisingly discovered that administering an anti-VLA-4 antibody significantly reduced the incidence of diabetes in a rodent model of diabetes (p. 4, lines 25-31). It appears that the enablement of the claimed invention is based on a hypothesis that since anti-VLA-4 antibody successfully delays diabetes in the NOD mouse model (and given the known facts that self-antigen reactive T cells play a key role in development of diabetes, that macrophages, T-cells and dendritic cells are associated with insulitis, that T-cells and macrophages express VLA-4 and dendritic cells express VCAM and VLA-4), that a fibronectin polypeptide that is known to bind VLA-4 (and therefore expected to block binding of VLA-4 to its ligand, inhibiting T-cell, macrophage, dendritic cell migration as well as T cell activation and development) will also successfully delay diabetes in the NOD mouse model. Given the surprising nature of the discovery, it cannot be predicted nor would it be expected that VLA-4 molecules other than the anti-VLA-4 antibody would function in the same manner.

In particular, although Example 5 purports to demonstrate that a VCAM-1/Ig fusion construct which binds BLA-4, successfully delays onset of diabetes in an adoptive transfer method wherein the specification states that treatment with the VCAM construct significantly delays development of diabetes with 60% of the animals developing diabetes at 30 days, when compared to the untreated transfer control (see Figure 1), the delay is only 7 days, with 60% of the transfer control animals developing diabetes at 21 days. The claims are drawn to "effective" treatment. It is not clear from the data presented in these experiments that this treatment is "effective". It appears that, similar to the findings reported on page 3, these subjects cannot maintain a non-diabetic state using this method of treatment. When comparing peptide fusion construct and antibody adoptive transfer experiments it becomes clear that although both constructs bind to VLA-4, the activity of the fusion construct is not the same as that of the antibody. With the fusion construct pretreatment, by day 30, 60% of the animals had developed diabetes, whereas with the antibody pretreatment, only 10% of the animals had developed diabetes by day 29/30. It is clear that the efficacy of the two constructs is not the same. Further, a review of the data appears to reveal a potentiating effect of the antibody isotype on delay of onset since the animals who received cells pretreated with the irrelevant isotype antibody clearly had delayed onset of diabetes compared to the animals who received non-treated cells (see Figure 1). On the other hand, the irrelevant fusion protein appears to have a potentiating effect upon diabetes onset wherein 60% of the recipient animals developed diabetes at day 15 after transfer while 60% of recipients with untreated donor cells did not develop

diabetes until day 21. Given the surprising nature of the antibody discovery, although reasonable to try to determine if other constructs function in the same manner, it is clear that the peptide fusion construct, despite its VLA-4 target, does not function in the same manner as the antibody, does not have the same efficacy as the antibody and that its successful use in a spontaneous diabetes model cannot be predicted. Further, although the peptide fusion studies appear to support the surprising nature of the antibody treatment discovery, they do not support extrapolation of the antibody findings to all VLA-4 binding moieties.

In addition, it is noted that the adoptive transfer experiments are clearly not commensurate in scope with the claimed invention since diabetes does not develop by adoptive transfer and diabetic cells are not conventionally pretreated with inhibitory constructs prior to insertion into a mammal.

Further, although delayed onset of diabetes with antibody administration in a spontaneous model (which is certainly more similar to the human condition) was exemplified and similar to the adoptive transfer experiments showed successful delay, given the differences in efficacy between the adoptive transfer experiments using the peptide fusion construct and the antibody, the effects of the construct on delay of diabetes incidence in a spontaneous model could not be predicted. Certainly, given the differences in structure, solubility and *in vivo* life expected between the claimed polypeptide and the exemplified constructs, since the difference in efficacy between the antibody and peptide fusion construct are so great, it could not be predicted, nor would it be expected that a soluble fibronectin polypeptide, which reads on a polypeptide, for example, of 3 amino acids, would

function as claimed based on the poor efficacy of the 555 amino acid peptide fusion construct compared to the successful antibody construct, regardless of the fact that the antibody, VCAM and fibronectin all bind to VLA-4.

Further, Examiner takes note of the art known differences between the stability of antibody molecules and polypeptides in the *in vivo* environment. The specification clearly recognizes the known differences when it teaches that VCAM-1 is a VLA-4 binding moiety and teaches that it may be bound to a second peptide, Ig, that increases solubility or *in vivo* time of the VLA-4 targeting moiety. molecules comprising VCAM-1 (p. 9, lines 26-35). It is noted that since the anti-VLA-4 antibody exemplified in Examples 1 and 4 is an antibody, given the information in the specification it is clearly more soluble and stable than a polypeptide. Although the specification teaches that VCAM polypeptide alone will function in the invention, it is clear that Applicant opted for potentiating both solubility and *in vivo* time of the VCAM for the exemplified experiment and despite the increased solubility and *in vivo* time imparted by the formulation, it does not appear that one of skill in the art would believe it more likely than not that the exemplified method would support the enablement of the peptide fusion construct for the treatment of insulin dependent diabetes in either prediabetic mammals or mammals with partial beta cell destruction based on the information in the specification.

Neither the successful anti-VLA4 antibody nor the VCAM-Ig construct are commensurate in scope with the claimed invention and the findings drawn to these constructs cannot be extrapolated to the enablement of the claimed invention given

that the claimed fibronectin polypeptides are not fused with any secondary peptides in order to increase their solubility and *in vivo* time, given that the claimed polypeptides reads on a three amino acid construct, given that even with fusion to Ig (the Ig portion of which appears to potentiate onset in the absence of the VCAM peptide moiety), the VCAM-Ig construct data does not appear to support a role for the construct in the treatment of insulin dependent diabetes, effective delay of onset in prediabetic individuals or individuals with partial beta cell destruction. Given the above, it would not be expected and could not be predicted that a fibronectin polypeptide would function as claimed based on the information in the specification. Further, given that the specification specifically teaches that treatment protocols after onset of disease are particularly problematic since at the time diabetes is diagnosed in humans, insulitis has typically progressed to a loss of more than 80%/90% of the beta cells, it is not clear how the claimed fibronectin polypeptides would be effective in treating individuals with partial beta cell destruction since individuals with partial beta cell destruction clearly have clinical diabetes.

Finally, as drawn specifically to claim 32, the claim is drawn to a method wherein the fibronectin polypeptide is conjugated to a toxin moiety. It is clear, that as taught by the specification, that fibronectin binds to VLA-4 which is expressed on T-lymphocytes, macrophages and dendritic cells.Although it would be expected that the binding of fibronectin polypeptide conjugated to a toxin moiety would destroy not only the cells to which it binds but also cells in the vicinity of the toxin, it is also clear that cells expressing VLA-4 are ubiquitous in the human body. Given the ubiquitous expression of VLA-4, although general immune suppression due to

the killing of immune cells would be expected, it is not clear how this general immune suppression would be effective to treat diabetes as claimed, especially in view of Applicant's statement in the Appeal Brief, page 5 wherein Applicant states that

> "Pages 3-4 of the background describe the shortcomings of prior art methods and compositions in treating diabetes. Unlike the generally non-specific modalities to treat diabetes described.....the present invention demonstrated how specific inhibitors of VLA-4-VCAM interactions effectively prevented immune cell destriuction of pancreatic islet beta cells and thus could be used to therapeutically treat diabetes"

It appears that claim 32 is drawn to general immune suppression which, although directed to a specific interaction, is clearly a non-specific modality and which would therefore be expected to have the shortcomings of prior art methods and compositions in treating diabetes. Therefore it could not be predicted that the invention could function as claimed.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that method would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention. Applicant is invited to submit objective evidence demonstrating that the invention functions as claimed.

Applicant's arguments drawn to the rejection of claims 25, 28 and 31-36 in Paper No. 17, section 7 pages 5-7 are relevant to the instant rejection.

Applicant argues that fibronectin polypeptides were known inhibitors of the VLA-4 activity and once the Appellant established the correlation between inhibition of the VLA-4-VCAM interaction and the treatment of diabetes, similar results were expected using fibronectin polypeptide.

The argument has been considered but has not been found persuasive because, for the reasons set forth above, although a correlation between inhibition of the VLA-4-VCAM by anti-VLA-4 antibody and the delayed onset of diabetes has been established, the specification clearly states that this is a surprising result. Further, for the reasons set forth above, a correlation between inhibition of VLA-4-VCAM, by constructs other than by anti-VLA-4 antibody, and the treatment of diabetes has not been established, especially in view of the marked differences of effectiveness of the anti-VLA-4 antibody and the fusion construct.

Applicant argues that both the anti-VLA-4 antibody studies and the VCAM/Ig studies demonstrated the successful reduction of diabetes in rodents, wherein the onset of diabetes was inhibited. The argument has been considered but has not been found persuasive because although it is clear that the anti-VLA-4 antibody functions successfully to delay onset of insulin dependent diabetes in a spontaneous diabetes model which mimics some of the aspects of human diabetes, the same cannot be said for the VCAM/Ig adoptive transfer studies. This is because the exemplified method does not in any way mimic any natural form of diabetes and further because the short term delay in onset of the diabetes, when compared with the adoptive transfer experiments with anti-VLA-4 antibody, would not support the enablement of an effective treatment of diabetes comprising that construct in a

spontaneous diabetes model and would not support the enablement of an effective treatment of diabetes comprising administration of a fibronectin polypeptide, which is not treated to increase solubility or *in vivo* life, in either in a prediabetic individual, an individual with partial beta cell destruction or an individual after the onset of diabetes for the reasons set forth above, especially in view of the marked differences of effectiveness demonstrated for the anti-VLA-4 antibody and the polypeptide fusion construct with increased solubility and *in vivo* life.

Applicant further argues that fibronectin and VCAM were known to be capable of binding to VLA-4 and fibronectin was known to inhibit VLA-4 activity both *in vitro* and in *in vivo* models and once the Appellant established the correlation between inhibition of the VLA-4-VCAM interaction and the treatment of diabetes, similar results were expected using fibronectin polypeptides. The argument has been considered but has not been found persuasive because similar results would not be expected for the reasons set forth above.

Applicant points to numerous references involving antibody and/or CS-1 peptide inhibitors of the VLA-4 interactions with VCAM or fibronectin to support the extrapolation of the instant findings from the VCAM/Ig construct studies to the enablement of the invention as claimed. The argument has been considered but has not been found persuasive for the reasons set forth above.

Applicant argues that although there was limited success in treating diabetes prior to the instant application, the treatment of diabetes with the instant method is not unpredictable because the present invention demonstrated how specific inhibitors of VLA-4-VCAM interactions effectively prevented immune cell

destruction of pancreatic islet beta cells and thus could be used therapeutically to treat diabetes. The argument has been considered but has not been found persuasive because the short-term demonstrated delay of onset in the adoptive transfer experiment disclosed is not supportive of the enablement of effective treatment of insulin dependent diabetes as claimed for the reasons set forth above.

11. If Applicant were able to overcome the rejections set forth previously and above, Claims 25, 31-36 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the recited method wherein soluble fibronectin polypeptide comprising an EILVD motif is administered, does not reasonably provide enablement for said method wherein a soluble fibronectin polypeptide, an alternatively spliced non-type III connecting segment of fibronectin, is administered. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to the recited method wherein a composition comprising a soluble fibronectin polypeptide is administered. This includes any fibronectin polypeptide, regardless of size.

The specification teaches a method of treating insulin dependent diabetes comprising the step of administering a VLA-4 blocking agent, fibronectin (p. 5, lines 8-20) that can be any naturally occurring VLA-4 ligand including fibronectin, fibronectin having an alternatively spliced non-type III connecting segment and fibronectin peptides containing the amino acid sequence EILDV or a similar conservatively substituted amino acid sequence (p. 9, lines 33-36).

One cannot extrapolate the teaching of the specification to the scope of the claims because Wayner et al (J. Cell Biol., 1989, 109:1321-1330) specifically teaches that fibronectin has a single VLA-4 binding site and that site is found in the type III connecting segment (see abstract). Further, Kaneda et al, Anti-Cancer Drugs, 1997, 8:702-707) specifically teaches that the type III connecting segment comprises the EILDV motif (see p. 702) and that there are only two major domains that play a role in cell adhesion (that is binding), one of which is an RGDS sequence and the other comprises EILDV. Although the specification has disclosed the non type III connecting segment, the specification does not define the segment, does not state that the segment comprises the only known binding motif of EILDV. Since the art clearly teaches that the VLA-4 binding site of fibronectin is found only in the type III connecting segment, given the lack of guidance in the specification, the lack of working examples, the information in the art, it cannot be predicted and would not be expected a non-type III connecting segment would function as claimed. Finally, Applicant admits on the record that the VLA-4 binding site of fibronectin is found in CS1 motif in the alternate spliced type IIICS (see p. 4 of Appeal Brief).

Further, Applicant has not revealed any VLA-4 binding motif in fibronectin other than the EILDV, thus no one of skill in the art would believe that it would be more likely than not that a fibronectin polypeptide, other than one comprising the EILDV motif would function as claimed. In addition, Kenda et al specifically teach that although an EILDV and ILDV peptide markedly inhibited adhesion of cells (apparently through blocking of the VLA-4 binding site), the EILD and ILD were only slightly inhibitory and LDV was inactive (see abstract). Since the mechanism

of action of the claimed fibronectin polypeptide of the instant invention is as a VLA-4 blocking agent wherein VLA-4 is blocked by competing with cell surface binding protein for VLA-4 (p. 5, lines 15-21), and since the mechanism of action of the prior art fibronectin polypeptide is by blocking cell adhesion which is apparently mediated by competing with cell surface binding protein for VLA-4, it could not be predicted, nor would it be expected that any of the EILD, ILD or LDV fibronectin polypeptides, which are encompassed by the instant claims, would function as claimed. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the method would function as broadly claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

12. In the interests of compact prosecution, if Applicant were able to overcome the rejections set forth above and if Applicant were to amend the claims to delete reference to a method of treatment of insulin dependent diabetes and substitute therefor a method of delaying onset of insulin dependent diabetes, claims 25, 28, 31-36 would still be rejected under 35 USC 112, first paragraph because the specification, while being enabling for a method of delaying onset of diabetes in a mammal, that is not a human, with a genetic susceptibility to diabetes or a mammal, that is not a human, having partial beta cell destruction wherein onset of diabetes has not occurred comprising administering a soluble fibronectin polypeptide in an amount effective to treat diabetes, does not reasonably provide enablement for a

method for delaying onset of diabetes in a prediabetic mammal or a mammal having partial beta cell destruction comprising administering a soluble fibronectin polypeptide in an amount effective to treat diabetes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method for the treatment of insulin dependent diabetes comprising administering to a prediabetic mammal or a mammal having partial beta cell destruction a composition comprising a soluble fibronectin polypeptide in an amount effective to treat diabetes. This includes the treatment of diabetes in mammals, humans, that don't have diabetes and treatment of diabetes in mammals, humans with clinical diabetes, that is humans with partial beta cell destruction. The specification teaches that treatment protocols after onset of disease are particularly problematic since at the time diabetes is diagnosed in humans, insulitis (which is the selective targeting and destruction of beta cells by an inflammatory cellular infiltrate of the pancreas) has typically progressed to a loss of more than 80% of the beta cells and so few beta cells may be present that even with prevention of further beta cell destruction, so few beta cells may be present that they cannot maintain a non-diabetic state over time (p. 3). Further, diabetes onset or clinical manifestation of the disease is at Stage V of development when approximately 90% of pancreatic beta cells are destroyed (p. 1, lines 31-35). The specification teaches that there has been little success in treating human diabetes and there is a need for immunosuppressive components for use in the prediabetic stage (page 4). The specification further teaches that a key role in the development

of diabetes is generally recognized for self-antigen reactive T cells and that in addition to T lymphocytes, insulitis is characterized by macrophages, dendritic cells and B cells, thus autoimmune diabetes relies upon both cellular migration and immune stimulation of newly resident cells. Cell trafficking to inflammatory sites is regulated by VLA-4 on the surface of lymphocytes and macrophages and by its counter-ligand VCAM on vascular endothelium and dendritic cells. Functional data indicates a role for VLA-4 in T cell activation. In additional, VLA-4 binds to fibronectin. The ability of VLA-4 to control cell migration to inflammatory sites *in vivo* has been directly demonstrated with monoclonal antibodies to VLA-4 (p. 2, lines 3-32). Current treatment protocols suggested for type I diabetes have included immunomodulatory drugs, wherein T cell activation and development are impaired. A long prediabetic period with immunologic abnormalities and progressive beta cell destruction suggests that it may be possible to halt beta cell loss with immune intervention (p. 3, lines 13-22). Since immunosuppressive mechanisms may prevent insulitis and/or diabetes, there is a need for immunosuppressive components for use in the prediabetic stage, in particular, there is a need for compounds which inhibit entry of effector cells into the pancreas or function of those cells which have already entered the islets (p. 4, lines 20-24). It has been surprisingly discovered that administration of anti-VLA-4 antibody reduced the incidence of diabetes in the NOD mouse model of diabetes (p.4, lines 25-26).

One cannot extrapolate the teaching of the specification to the scope of the claims because the difficulties in treating clinical diabetes (wherein beta cell destruction is partial) and human diabetes, acknowledged by Applicant in the

specification, are well known in the art. For example, Tisch et al (PNAS, 1994, 91: 437-438), of record, specifically teach that insulin-dependent diabetes is a T-cell-mediated autoimmune disease. Tisch et al specifically state that the most critical factor in treating autoimmune disease is whether the therapy can be used to treat an ongoing autoimmune response or whether it is effective only in terms of prevention. (It is clear that there has been no demonstration in the specification that the method as claimed would be effective to treat ongoing insulin-dependent diabetes) Typically, an autoimmune disease is diagnosed at a time when significant tissue damage has already occurred. At this point, the need is for a form of therapy that can prevent further tissue damage and eliminate or block all or nearly all autoreactive T cells (para bridging columns 2 and 3). Tisch et al further point to the difficulty in treating insulin-dependent diabetes because it is known that T-cells have been activated against as many as six to eight autoantigens and the critical inciting autoantigens are not known (column 3). In view of the known lack of success in treating insulin-dependent diabetes and the critical requirement of determining whether a treatment can be used to treat an ongoing autoimmune response as taught by Tisch et al, it cannot be predicted, based on the information in the specification and the art, that the invention will function as claimed.

Further, the claims, if amended would still not be enabled to delaying onset of diabetes in a human because it is well known in the art that although NOD mice are known as a mouse model for type 1 diabetes, as taught by Atkinson et al (Nature Medicine, 1999, 5:601-604), of record, when NOD mice are used as a surrogate for humans, genus-specific differences that restrict the interpretation of results of

experiments are unavoidable (p. 601, col 1). In NOD mice, type 1 diabetes development is well-choreographed when all the relevant environmental factors are held constant. Specific windows can be defined in which an immunomodulator can be either protective or destructive In contrast, the natural history of type 1 diabetes in humans is such that the age of disease onset is extremely broad, symptoms may occur at any time from the first years of life to well beyond 50 years of age. Atkinson et al further caution that studies analyzing therapeutic agents aimed at delaying/preventing type 1 diabetes in NOD mice must be carefully assessed for their functional as well as their practical applicability to therapeutic intervention in human disease. For example, agents used in NOD mice from birth may not be applicable to treatment of humans identified immediately before the onset of type 1 diabetes. It is clear that the genus-unique and strain-specific aspects of diabetogenesis in NOD mice must be fully understood and appreciated if we are to know which therapeutic protocols are reasonable to extrapolate to humans and which are not (p. 603, cols 1 and 2). Although as of early 1999, more than 125 individual methods for the prevention or delay of type 1 diabetes in NOD mice had been reported (para bridging pages 602-603), Atkinson et al teach that it is clear that the course of type 1 diabetes development in randomly breeding humans will not be as easily deviated as it is in highly inbred rodent models in which genetic risk is a constant such that interventions can be initiated at very early stages of pathogenesis (p. 604, col 2). Finally, even if it were to be demonstrated that fibronectin polypeptides were effective at delaying or preventing onset of diabetes in NOD mice, the specification does not teach, give guidance on or provide working

examples that would provide guidance to one of skill in the art as to when fibronectin should be administered to the broadly claimed mammals. Clearly, as taught by Atkinson et al, the age of onset of human diabetes ranges from the first years of life to well beyond fifty years of age. Further, although it is known that there is a population of human mammals at risk for developing type 1 diabetes, it is also known that not all of the members of that population develop the disease and it cannot be predicted which member of that population will develop the disease because of the genetic and environmental heterogeneity associated with the natural history of the disease. In comparing the heterogeneous human population with NOD mice, Atkinson et al specifically states that there is little evidence that many of the individuals at high risk for type 1 diabetes development would have a set of immune deficiencies that would prove as malleable as those of the highly inbred NOD mouse rodent population (p. 603, col 1). As taught by Bowman et al (Immunology Today, 1994, Vol 15:115-120), of record, given the genetic heterogeneity within the human population, the development of insulin-dependent diabetes is likely to reflect heterogeneous mixtures of susceptibility genes whose penetrances are responsive to different thresholds of intragenic and environmental influences and that given these complexities it has thus been difficult for clinical investigators to develop diagnostic tools for the early identification of humans destined to develop insulin-dependent diabetes (p. 115, col 2).

The specification provides insufficient guidance with regard to these issues. and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art

to practice the claimed invention with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

13. All other objections and rejections recited in Paper No. 17 are withdrawn.

14. No claims allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
May 15, 2003